REMARKS

Claims 1-7, 9 and 15 are canceled. The Examiner has rejected Claims 8-14. In this response, Applicants have added new Claims 16-21. Therefore, as of entry of this amendment, Claims 8, 10-14 and 16-21 will be pending.

Objection to the Specification

The Examiner has objected to the specification for allegedly not incorporating SEQ ID NO's when referring to nucleic acid or amino acid sequences. Applicants have amended the specification to add SEQ ID NOs in the Brief Description of the Figures and included a replacement Sequence Listing. Applicants therefore respectfully request that the Examiner withdraw the objection to the specification.

Claim Rejections Under 35 U.S.C. § 112, first paragraph, Written Description

Claims 8-10 and 12-14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, more specifically as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

Applicants respectfully submit that adequate written description is provided to convey that the inventors, at the time of filing, had possession of the claimed invention.

The Examiner has asserted that "Applicants do not identify essential regions of the genus of protein having an ARF GAP domain wherein the protein is involved in organ loss. Applicants respectfully disagree with this assertion. The present claims are limited to the *NEVERSHED* gene which the inventors have fully disclosed in the specification. The inventors have demonstrated that the *NEVERSHED* gene is involved in floral organ loss as is presently claimed. Furthermore, the present application provides relevant guidance that would assist one of skill in the art in determining that the inventors were in possession of mutations in the *NEVERSHED* gene that prevent floral organ loss. By way of example, the specification teaches

nev-2, which involves a premature stop codon at amino acid 197. In addition, the specification teaches *nev-1*, which involves mutation of one of the highly conserved residues in the ARF GAP domain. Form these two mutations, one of skill in the art would appreciate that these mutations both inactivate the ARF GAP domain. Therefore, from these two mutations that inventors teach, one of skill in the art would recognize that any premature stop codon placed at amino acid 197 or N-terminal to amino acid 197 in the ARF GAP domain would also achieve the desired phenotype. Furthermore, the specification includes an alignment with other ARF GAP domains showing the conserved amino acids. In addition, simply knocking out the gene using readily available technology and thereby removing the ARF GAP domain entirely would achieve the desired phenotype. Also, one of skill in the art would recognize that residues that are conserved across species as widely divergent as plant and animal species must be important for function and the mutation of such residues are likely to inactivate the protein thereby producing the claimed phenotype. One of skill in the art would therefore have no difficulty in identifying a large number of mutations that would inactivate the ARF GAP domain and thereby achieve the desired phenotype from the teaching of the specification alone.

Second, as of the filing of the application, the ARF GAP domain was a known domain with an assigned function, with a significant amount of data obtained as to its function and the structures of a number ARF GAP domains had been determined (see, *e.g.*, Jensen *et al.* (2000, Plant Molecular Biology 44:799-814)). All of this information can be used by one of skill in the art to determine additional mutations that will inactivate ARF GAP domains and therefore one of skill in the art would recognize that the inventors had possession of the presently claimed invention as of the filing of the application. Thus, there is structural information linked to functional information in the art.

The Examiner has relied upon *University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997) in support of the written description rejection. However, compliance with the written description is a fact based analysis, not a legal analysis and therefore case law is only relevant to the extent that the facts are the same or similar. The present claims are different in significant ways. The claims at issue were to plasmids or vectors encoding functional proteins (insulin and human pre-proinsulin) with any number of mutations ***while maintaining function***. The

present claims are directed to the *NEVERSHED* gene in the allelic forms as it exists in plants. As discussed above, the mutations in the present claims are intended to ***inactivate*** the ARF GAP domain so as to convey a phenotype. Mutating a gene to inactivate the protein is much more predictable than mutating the gene while maintaining the protein's activity. Second, the patents that the Federal Circuit was evaluating were filed in May 1977 and September 1979, respectively while the present application was filed in November 2001, more than twenty years later. Written description is evaluated in light of what one of skill in the art would understand that the inventor was in possession of ***at the time the application was filed***. In the intervening time, the knowledge of one of skill in the art has advanced at an incredible rate such that a large amount of data is available including entire genomes from several species and data on the function and structure of ARF GAP domains in particular. Thus the conclusion that the Federal Circuit reached in 1979 is not terribly relevant to the state of the art in 2001. The fact that in 1979 one of skill in the art could not have predicted the scope of ***active*** insulin and pro-insulin coding plasmids and vectors is not relevant to the present situation where the skill in the art is much more advanced.

However, even if *Eli Lilly* were a per se rule of law, Applicants have satisfied both prongs. The inventors have disclosed two mutations that provide the claimed phenotype both of which will allow one of skill in the art to readily predict several additional mutations that will provide the claimed phenotype. Therefore, the applicants have disclosed a representative number of *NEVERSHED* genes with the mutations as claimed. In addition, as noted by the Examiner, the structure of the ARF GAP domain was known and *nev-1* mutation demonstrates that disruption of the zinc finger structure of the ARF GAP domain is a common structural feature of the claimed mutation in the ARF GAP domain. Therefore, one of skill in the art would recognize that the inventors were in possession of the claimed invention.

Thus applicants respectfully request that the Examiner withdraw the rejection of claims 8-10 and 12-14.

In addition, applicants respectfully assert that the written description rejection made by the Examiner should not be applied to new claims 16-18 and 20-22 for the reasons discussed above. In addition, the new claims include the recitation "further comprising determining if said mutation results in prevention of floral organ loss in said plant." This recitation clearly addresses the

Examiner's assertion that "Applicants fail to describe a representative number of polynucleotide sequences encoding a protein having an ARF GAP domain, wherein the mutant protein is involved in preventing organ loss on the plant." In claims 16-18 and 20-22, the method clearly involves a step of screening for the result. Thus, it is irrelevant whether one of skill in the art could predict whether any given mutation would produce the desired phenotype since the claimed method can be used to screen for the desired phenotype. Therefore, applicants respectfully assert that the new claims 16-22 satisfy the written description requirement.

Claim Rejections Under 35 U.S.C. § 112, first paragraph, Enablement

Claims 8-14 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for a method of preventing organ loss in any plant comprising mutating the ARF GAP domain of any gene in said plant.

Applicants respectfully traverse. The Examiner has asserted that the "[a]pplicants have not disclosed other proteins comprising an ARF GAP domain that can be mutated to produce the desired phenotype, other than mutating the nucleotide sequence of SEQ ID NO:1." The presently amended claims are now limited to mutating the *NEVERSHED* gene in a plant, thus rendering this ground for rejection moot. Applicants have disclosed the genomic portions of *NEVERSHED* in *Arabidopsis* as SEQ ID NO:7 and the cDNA of NEVERSHED as SEQ ID NO:1. One of skill in the art may readily use the disclosed sequences as probes to identify the corresponding gene in other plants. Also, the sequence alone may be used to screen databases with the genome sequences of other plants to identify homologs in other species. Techniques used for designing degenerate oligonucleotides for PCR were well developed as of the filing date of the present application and one of skill in the art can use the sequence alignment provided in Figure 2 to determine what regions of the ARF GAP domain of *NEVERSHED* are likely to be conserved in order to design such degenerate oligos.

The Examiner has asserted that the "[a]pplicants have not disclosed preventing any organ loss, other than preventing sepals, petals and stamens from abscising by mutating SEQ ID

NO:1." The presently amended claims are now limited to preventing floral organ loss, thus rendering this ground for rejection moot. The applicants have demonstrated that mutations in *NEVERSHED* prevent floral organ loss.

The invention has clearly been enabled of the full scope as presently claimed given the disclosure in the specification and the state of the prior art as of the priority date of the present application.

To be enabled, one of skill in the art must be able to make and use the claimed invention without undue experimentation. The relevant factors to be considered when evaluating whether undue experimentation is required are: (1) the state of the prior art; (2) the level of predictability of the prior art; (3) the amount of direction provided by the inventor; (4) the presence of working examples; (5) the skill in the art; (6) the amount of experimentation required; and (7) breadth of the claims.

With regard to the state of the prior art and the level of predictability in the prior art, as discussed above regarding the written description requirement, the predictability is greater than is typically found in biotechnology related patent applications. The present claims are direct to methods that involve inactivating a protein domain rather than mutations that maintain activity. One of skill in the art can very easily identify mutations that inactivate the NEVERSHED protein ARF GAP domain, particularly in light of the disclosure in the application. In addition, the state of the art is quite high regarding introducing such mutations into plants. Therefore, both of these factors indicate that undue experimentation is not required. In addition, the ARF GAP domain is a known protein domain that has been studied extensively. All of this knowledge regarding the structure and function of ARF GAP domains will inform one of skill in the art as to how to mutate the ARF GAP domain in a manner that will inactivate it.

Regarding the amount of direction provided by the inventor and the existence of working examples, the specification includes two examples demonstrating mutations in the ARF GAP domain of the *NEVERSHED* gene that produce the desired result. In one instance, the mutation is a

premature termination. One of skill in the art would recognize that introduction of a premature termination at the same place or anywhere N-terminal of the site would result in the desired phenotype. In the second instance, the mutation is in one of the conserved residues of the ARF GAP domain. Figure 2 shows the other conserved residues in the ARF GAP domain, all of which are likely targets for the mutation. These two working examples are sufficient guidance given the relatively advanced status of the art and the high predictability.

Regarding the skill in the art, one of skill in the art in this instance has a very high level of skill given that mutating plants can involve transformation which, while increasingly routine, is typically carried out by scientists at the graduate level or higher. Scientists at the graduate level or higher are readily familiar with the molecular biology techniques involved in introduction of mutations into particular genes in plants. Further, testing such plants for lack of floral organ loss is a routine task readily within the skills of scientists at the graduate level or higher.

Regarding the amount of experimentation required, relatively little experimentation will be required. As discussed above, all that is required to practice the invention is to inactivate the ARF GAP domain of the NEVERSHED protein. Given the examples, one of skill in the art would have no difficulty in identifying at least two mutations that will inactivate the protein because the specification provides the two mutations. From those two examples, one of skill in the art would easily be able to identify a large number of additional mutations that would yield the claimed phenotype.

Regarding breadth of the claims, the claims are reasonably narrow as they are limited to mutating the *NEVERSHED* gene which is disclosed in the application and limited to the phenotype of preventing floral organ loss which has been demonstrated in the application. Given the high level of predictability and the advanced state of the art, the disclosure is more than sufficient to enable one of ordinary skill in the art to make and use the presently claimed invention.

Applicants respectfully request that the Examiner withdraw the rejection of claims 8-14.

With regard to the new claims 16-21, the practice of the claimed invention requires even less experimentation as the claims include a screening step for phenotype. Thus, one of skill in the art does not need to have any knowledge of how to inactivate the protein and therefore the practice of the invention is not just highly predictable, it is completely predictable. Can one of skill in the art introduce a mutation into the ARF GAP domain of the *NEVERSHED* gene – of course. Can one of skill in the art screen for prevention of floral organ loss – of course.. Thus, the applicants respectfully assert that the enablement rejection is not applicable to claims 16-21.

Claims 8-14 free of the prior art

Applicants thank the Examiner for noting that pending claims 8-14 are free of the prior art.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 532792001100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 3, 2006

Respectfully submitted,

By _____

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